Contribution of EEG/fMRI to the definition of the epileptic focus

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ABSTRACT

Objectives: To evaluate the clinical relevance of EEG/fMRI in patients with focal epilepsy, by assessing the information it adds to the scalp EEG in the definition of the epileptic focus.

Methods: Forty-three patients with focal epilepsy were studied with EEG/fMRI using a 3-T scanner. Blood oxygen level–dependent (BOLD) signal changes related to interictal epileptic discharges (IEDs) were classified as concordant or not concordant with the scalp EEG spike field and as contributory if the BOLD signal provided additional information to the scalp EEG about the epileptic focus or not contributory if it did not. We considered patients having intracerebral EEG or a focal lesion on MRI as having independent validation.

Results: Thirty-three patients had at least 3 IEDs during the EEG/fMRI acquisition (active EEG), and all had a BOLD response. In 29 of 33 (88%) patients, the BOLD response was concordant, and in 21 of 33 (64%) patients, the BOLD response was contributory. Fourteen patients had an independent validation: in 12 of these 14, the BOLD responses were validated and in 2 they were invalidated.

Conclusions: A BOLD response was present in all patients with active EEG, and more specific localization of the epileptic focus was gained from EEG/fMRI in half of the patients who were scanned, when compared with scalp EEG alone. This study demonstrates that EEG/fMRI, in the context of a clinical practice, may contribute to the localization of the interictal epileptic generator in patients with focal epilepsy. ***Neurology*® 2012;78:1479–1487**

GLOSSARY

BOLD = blood oxygen level–dependent; **EPI** = echoplanar imaging; **FCD** = focal cortical dysplasia; **IED** = interictal epileptic discharge; **MTS** = mesial temporal lobe sclerosis; **SEEG** = stereo-EEG; **TE** = echo time; **TR** = repetition time.

Recording fMRI and EEG simultaneously is a noninvasive method detecting cerebral hemodynamic changes related to interictal epileptic discharges (IEDs) on scalp EEG. Several studies demonstrated the ability of EEG/fMRI to characterize various forms of focal and generalized epilepsy.[1,2] In patients with focal epilepsy, especially those who are pharmacoresistant and surgical candidates, the significant clinical question is how the blood oxygenation level–dependent (BOLD) changes related to IEDs can contribute to localize the epileptic focus. The BOLD signal usually increases in regions generating focal IEDs,[3] but often in the context of more widespread, or even distant, responses.[4] Simultaneous intracranial EEG/fMRI recordings[5] have shown IED-related BOLD changes in the immediate vicinity of the intracranial EEG focus, confirming spatial concordance between neuronal and BOLD changes. Distant BOLD changes related to specific IED patterns were also observed. EEG/fMRI may help in the evaluation of patients who are candidates for surgery[6] and, in patients with nonlesional frontal lobe epilepsy, EEG/fMRI contributed to localize foci subsequently confirmed by other imaging modalities or pathology.[7] Finally, in a postsurgical population, it was shown that when the resection included the BOLD activation region, patients showed good outcome.[8]

In the current study, rather than assessing the validity of the BOLD response, which has largely been demonstrated, we examine the contribution of the BOLD response to localizing

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Supplemental Data

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the irritative zone; we wish to determine what new information EEG/fMRI adds to localizing the spike generator compared with EEG alone. We selected 43 patients with refractory focal epilepsy of various etiologies; we believe that the absence of any other selection criteria provides a good indication of the potential of EEG/fMRI in clinical practice.

METHODS

Subjects. We retrospectively included consecutive patients with a diagnosis of focal epilepsy who underwent EEG/fMRI from April 2009 to July 2010. Not all hospitalized patients fitting these criteria were scanned because of limited scanner availability or other logistic reasons related to performing a research study in a clinical context. Usually, patients were selected for an EEG/fMRI if they had frequent IEDs (spikes, polyspikes, or sharp waves) during a recent EEG. Some patients, with an unclear clinical situation, were scanned even if their EEG was not very active to try to help with their evaluation. EEG/fMRI results were not used to plan the placement of intracranial electrodes. Classification of epilepsy was made by 2 neurologists before fMRI analysis according to clinical information, electrophysiology, and structural MRI.[9]

Standard protocol approvals, registrations, and patient consents. The study was approved by the institutional research ethics board. Subjects gave written informed consent in accordance with the Research Ethics Committee of the Montreal Neurological Institute and Hospital.

EEG/fMRI acquisition. EEG was recorded inside a 3-T MRI scanner (Trio; Siemens, Erlangen, Germany) with 25 magnetic resonance−compatible electrodes (Ag/AgCl) placed on the scalp using 10–20 (reference FCz) and 10–10 (F9, T9, P9, F10, T10, and P10) electrode systems, with a BrainAmp system (Brain Products, Munich, Germany). The patient's head was immobilized with a pillow filled with foam microspheres to minimize movement and for comfort.

A T1-weighted anatomic acquisition was done (1-mm slices, 256 × 256 matrix, echo time [TE] = 7.4 msec, repetition time [TR] = 23 msec, flip angle 30°) and used to superimpose functional images. Functional data were acquired in 6-minute runs with patients at rest, using a T2*-weighted echoplanar imaging (EPI) sequence (64 × 64 matrix, 33 slices, 3.7 × 3.7 × 3.7 mm, TE = 25 msec, TR = 1.9 sec, flip angle 90°).

EEG/fMRI processing. ***EEG.*** Brain Vision Analyzer software (Brain Products) was used for correcting the gradient artifact.[10] The ballistocardiogram artifact was removed by independent component analysis.[11] For each patient, IEDs similar to those recorded outside the scanner were marked by a single electroencephalographer. IEDs with different morphology or distribution were analyzed as separate event types.

fMRI. EPI images underwent motion correction (realignment with 6-parameter rigid-body transformation) and smoothing (6-mm full width at half-maximum) using software from the Montreal Neurological Institute (http://www.bic.mni.mcgill.ca/ServicesSoftware/HomePage). Temporal autocorrelations were accounted for by fitting an autoregressive model of order 1,[12] and low-frequency drifts were modeled with a third-order polynomial. A regressor for each IED type was built using the timing and duration of each event and convolved with 4 hemodynamic response functions peaking at 3, 5, 7, and 9 seconds.[13] All regressors were included in the same general linear model. A study was performed for each interictal event type. A statistical t map was obtained for each regressor using the other regressors as confounds.[12] To account for residual movement artifacts, the movement parameters were included as confound regressors.

EEG/fMRI analysis. To be significant, a response required 5 contiguous voxels having a t value >3.1 corresponding to $p < 0.05$, corrected for multiple comparisons (family-wise error rate) due to the number of voxels and the 4 hemodynamic response functions. The t map results were displayed using a red-yellow scale for positive BOLD changes (activation) and a blue-white scale for negative BOLD changes (deactivation). Responses outside the brain parenchyma were ignored. BOLD responses related to each IED type were reviewed by 3 experts.

For each patient, the analysis proceeded as follows.

Concordance between EEG and fMRI. The spike field (the region thought to generate the spike) was estimated at the sublobar level by visual inspection of the scalp EEG (for example, F7-T3-T5 spikes generated in the anterior left temporal lobe or Fp1-F3-F7 spikes generated in the anterior left frontal lobe). Each BOLD response (positive and negative) for each type of IED was considered concordant if the maximum t value corresponded to the localization of the EEG spike field. If a patient had multiple activations or multiple deactivations, we selected only the response with the highest t value. We considered not concordant a BOLD response with a maximum t value outside the spike field.

Contribution of EEG/fMRI. BOLD responses were considered contributory if the BOLD response to at least one event type provided additional information to the EEG alone. The following conditions were considered to add information:

- BOLD response able to more accurately localize the cortical region responsible for the generation of a spike within a lobe (for example, BOLD response to F7-T3 spikes pinpointing to the anterior part of the left first temporal gyrus).
- BOLD response with maximum t value in deep brain structures likely to be, according to anatomo-electroclinical information, part of the epileptogenic zone (for example, the BOLD response to F7-T3 spikes with maximum in the left hippocampus).

BOLD responses were not contributory if not concordant with the spike field or if the concordant BOLD map provided no new information compared with that from the scalp EEG. We realize that these definitions are subjective, but we will clarify them by illustrating several cases.

To explore the role of the lesion in BOLD changes, we also compared the contribution of the BOLD response with structural MRI findings.

Independent validation of EEG/fMRI. Patients who underwent intracerebral EEG (stereo-EEG [SEEG]) with electrodes exploring the area of the BOLD response or patients with a focal lesion on MRI had an independent validation of the EEG/fMRI findings. A lesion was considered focal only when it was contained within a lobe. For instance, polymicrogyria, which usually encompasses more than one lobe could not provide independent validation. If the independent validation confirmed the BOLD data, the latter was validated (i.e., SEEG shows seizure onset in the same sublobe or MRI shows a focal lesion considered as an epileptic focus in the same lobe); if not, it was invalidated. Five patients had 2 EEG/fMRI sessions and in

all the studies provided the same BOLD results. We do not consider this repeatability as validation.

RESULTS Forty-three patients with focal epilepsy (16 male) were selected (mean age at evaluation 30.5 years, range 1−65 years; mean age at seizure onset 12.5 years, range 1−42 years). Ten patients were excluded from the study: in 9 the EEG was not active during EEG/fMRI acquisition and in 1 artifacts prevented the marking of abnormalities. The clinical data of the 33 patients studied are presented in table e-1 on the *Neurology*® Web site at www.neurology.org.

The epilepsy was unifocal in 27 patients and bifocal in 6 patients. Among these 33, 9 patients had bilateral diffuse EEG discharges.

MRI results were negative in 18 patients including 3 who had EEG/fMRI after surgery: 9 had a malformation of cortical development (plurilobar nodular heterotopia in 3, plurilobar polymicrogyria in 2, focal cortical dysplasia [FCD] in 2, lissencephaly and band heterotopia in 1, and hemimegalencephaly in 1); 4 had mesial temporal lobe sclerosis (MTS), 1 had bifrontal encephalomalacia, and 1 had an occipital cyst.

The 33 patients with active EEG during acquisition had at least 1 IED type: 1 type, 15 patients; 2 types, 16 patients; and 3 types, 2 patients. Therefore, a total of 53 EEG/fMRI studies were analyzed. Three to 1,380 IEDs were recorded during the fMRI session. fMRI results are presented in table e-2. Five EEG/fMRI studies showed no BOLD response, but this occurred in 5 patients with multiple types of IEDs. Hence, at least one BOLD response was observed for each patient, leaving 48 studies to analyze: 15 patients presented only activations, 4 patients presented only deactivations, and 29 patients presented activations and deactivations.

Concordance between BOLD response and spike field. In 29 of 33 patients (88%) at least one BOLD response was concordant (39 analyses) with the spike field (table e-2). The concordant responses were focal in 24 patients with focal discharges and diffuse in 5 patients with bilateral diffuse discharges. In the patients with focal discharges, the maximum *t* value corresponded to an activation in 20 (figures 1, 2, and 3) and a deactivation in 4 (figure 4). Less significant responses were found in the thalamus, anterior and posterior cingulate, or frontolateral and parietal areas. In the 5 patients with bilateral diffuse discharges (figure 5), the parietal areas or the precuneus or the posterior cingulate showed the highest deactivations (default mode regions), and the anterior cingulate or thalamus showed the highest activations.

In 4 of 33 patients (12%), the BOLD response was not concordant (5 analyses) with the spike field. In 3 (patients 1, 11, and 15), there was no BOLD activity in the spike field and responses were compatible with artifactual patterns. The fourth (patient 9) (figure e-1) had right temporal spikes with no BOLD response and left temporal spikes with widespread activation encompassing the spike field and deactivation suggesting the default mode network with a maximum *t* value in the left parietal cortex.

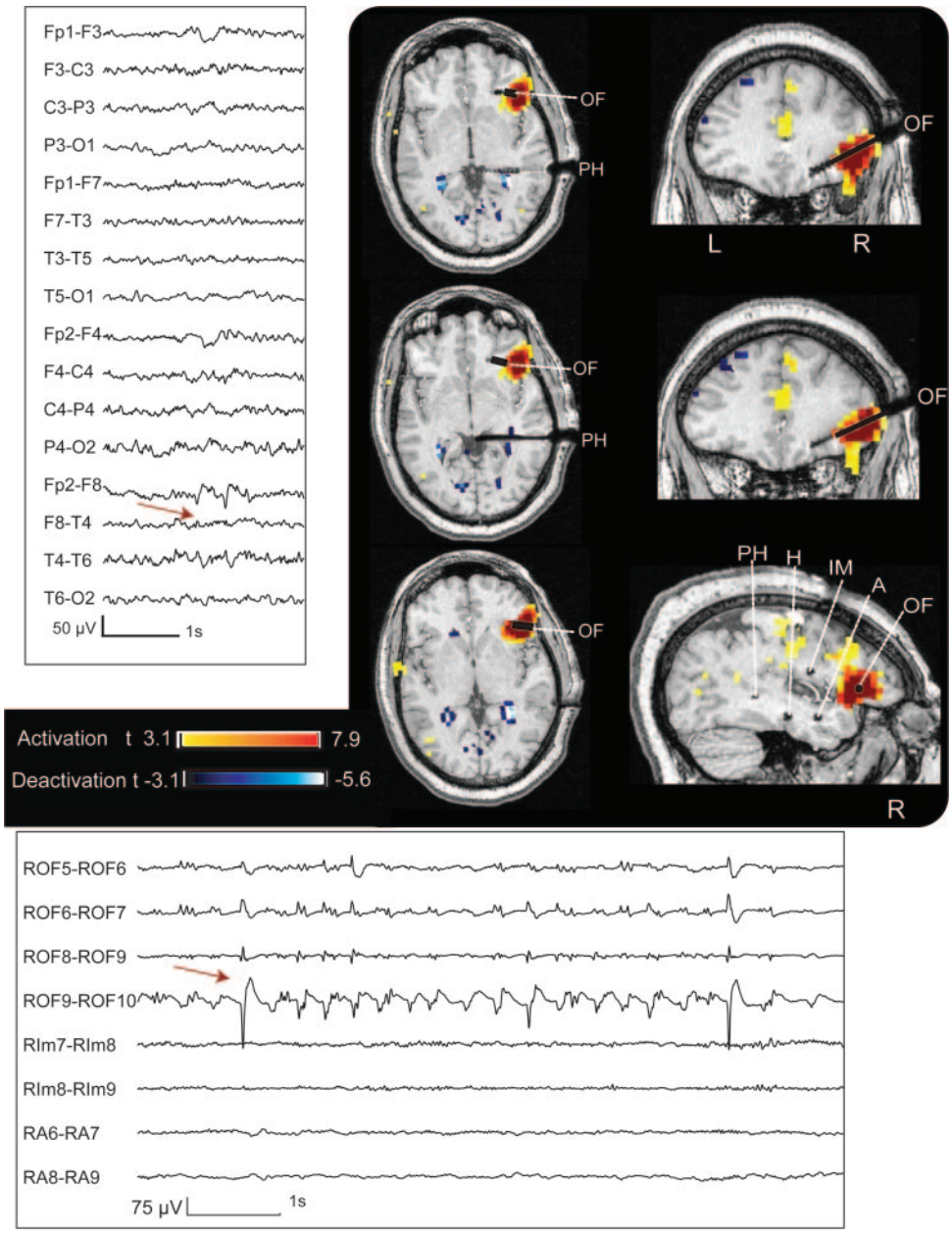
Contribution of BOLD responses to defining the epileptic focus. In 21 of 33 patients (64%) at least one BOLD response (24 analyses) was contributory (figures 1, 2, and 4). In 16 of 21 patients, the BOLD response was better than the EEG alone to determine the cortical region generating the spike within a lobe or a region (figure 1): frontal lobe in 7 (patients 2, 4, 16, 17, 19, 24, and 30), temporal lobe in 3 (patients 10, 20, and 32), parietal lobe in 3 (patients 5, 6, and 7), occipital lobe in 2 (patients 18 and 29), and temporo-parieto-occipital region in 1 (patient 25). In 5 of 21 patients, BOLD responses were maximum in deep brain structures likely to belong to the epileptogenic zone (figure 2): 2 patients with MTS (patients 12 and 14) showed a maximum activation in the amygdala and hippocampus and in 3 patients with nodular heterotopias (patients 21, 22, and 23), the maximum activation was in the heterotopic tissue.

In 12 of 33 patients (36%), the BOLD response (17 analyses) was not contributory. In 4 of 12 (patients 1, 9, 11, and 15), the BOLD response was not concordant (figure e-1) with the spike field and in 8 (patients 26, 27, 28, 31, and 33 with diffuse EEG discharges and patients 3, 8, and 13 with focal spikes), the BOLD response did not add new information compared with that for EEG alone (figures 3 and 5).

Regarding the relationship between the contribution of BOLD responses and structural MRI (table e-2), the BOLD response was concordant and contributory in 10 of 18 patients (55%) with focal epilepsy from an unknown cause, in 2 of 4 patients with MTS, and in 9 of 9 patients with a malformation of cortical development. The 2 patients with a bilateral frontal encephalomalacia or occipital cyst had bilateral diffuse IEDs and concordant but noncontributing BOLD responses.

Independent validation. Independent validation of EEG/fMRI findings was obtained in 14 patients (42.4%): 7 by SEEG alone, 4 by a focal lesion, and 3 by SEEG and a focal lesion (table e-2). All focal lesions were sublobar (4 MTS, 2 FCD, and 1 occipital cyst). In another patient (patient 20) with an extensive perisylvian polymicrogyria and SEEG, the maximum *t* value (middle first temporal gyrus) was anterior to the main epileptogenic area defined by SEEG, but no electrode was implanted in the maxi-

Figure 1 A 25-year-old patient (patient 17) with right frontal epilepsy

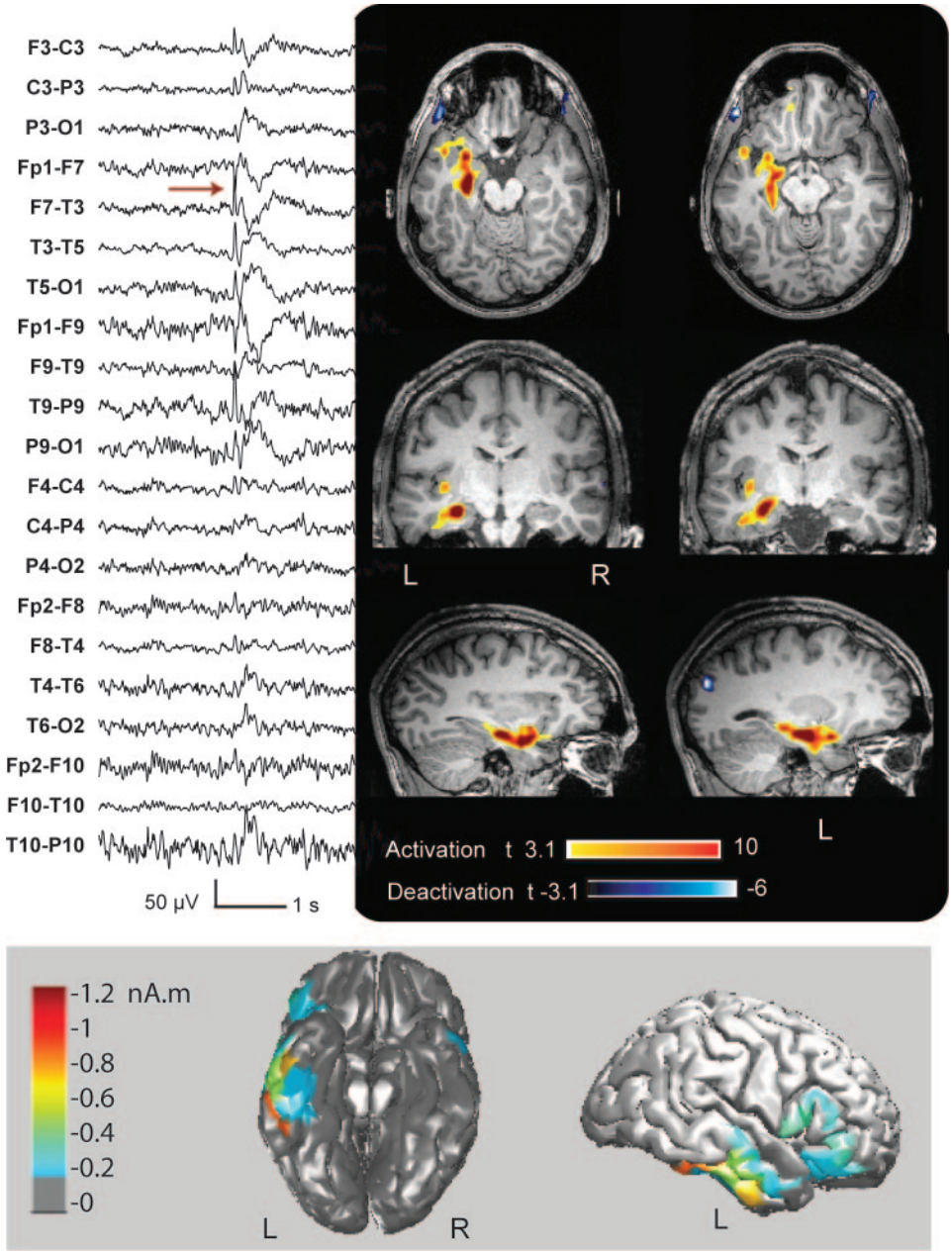


The marked events were Fp2-F8 spikes. The blood oxygen level–dependent (BOLD) response showed a limited activation in the lateral right orbitofrontal region. The patient underwent a depth electrode study. Five electrodes were inserted in the right hemisphere: one in the orbitofrontal region (OF), one aiming for the amygdala (A), one in the anterior hippocampus (H), one in the mid-insula (IM), and one in the posterior hippocampus and parahippocampus (PH). The black points and lines indicate the electrodes visible in these views and are obtained by coregistration with the BOLD map. The intracranial study revealed a very active epileptic generator in the lateral portion of the right orbitofrontal lobe (ROF6–ROF10). A limited right frontal corticectomy was performed and histology showed focal cortical dysplasia type 1. This is an example of a BOLD response considered concordant, contributory, and validated. Left: scalp EEG, bipolar montage, Fp2-F8 spikes. Right bottom: intracerebral stereo-EEG. Arrow indicates the interictal event thought to correspond to the scalp spike.

mum BOLD response; hence, the study could not be validated or invalidated.

In 9 of 14 patients, the BOLD responses was concordant and contributory, and in all these patients the BOLD response was validated. In 4 of 14 patients, the BOLD response was concordant but not contributory: in 3 it was validated and in 1 it was invalidated. The patient with the invalidated response (patient 13) had left MTS but only a neocortical left temporal activation (figure 3). Finally, in 1 of 14 patients (patient 15), the BOLD response (in the central regions) was not concordant with the spike field (temporal lobe), and the lesion (left MTS) invalidated the fMRI response.

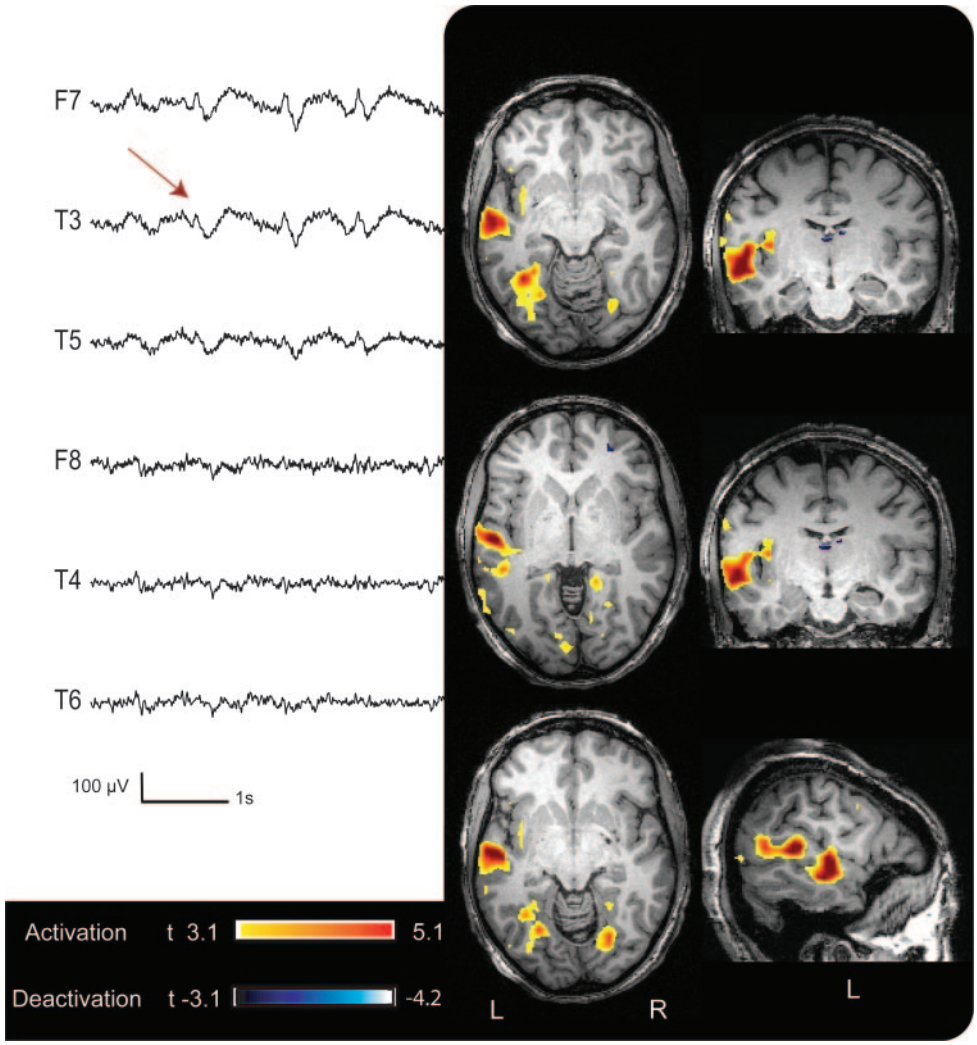
Figure 2 A 19-year-old patient (patient 14) with left temporal epilepsy and mesial temporal lobe sclerosis (MTS)



The marked events were F7-F9 spikes (bipolar montage), and the blood oxygen level–dependent (BOLD) response showed a focal activation in the left head and body of hippocampus. This response was considered concordant with the spike field and contributory, because it shows the involvement of a deep brain structure, suggested to be involved in the epileptic focus by the anatomo-electroclinical correlations and not visible from the scalp EEG. Because of the focal lesion (MTS), the BOLD response was considered validated. Bottom: source analysis of the same event (average of 13 spikes) projected on a head model of an averaged brain template (http://neuroimage.usc.edu/brainstorm/). The source estimation, provided by the maximum entropy on the mean, was in the middle part of the third neocortical temporal gyrus, confirming that the scalp spike is generated in the temporal neocortex.

In summary, in 21 patients (groups 1 and 2 of table e-2), the BOLD response was concordant with the spike field and contributory, providing new localizing information compared with that from scalp EEG alone. In 9 of these patients, the studies were validated and in 12 no independent validation could be obtained. In 8 other patients (groups 3 and 4), the BOLD response was concordant with the spike field but was not contributory; 3 of these studies were validated, 1 was invalidated, and 4 had no independent validation. Finally, in the remaining 4 patients (groups 5 and 6), the BOLD response was neither concordant nor contributory.

Figure 3 A 46-year-old patient (patient 13) with left temporal epilepsy and mesial temporal lobe sclerosis (MTS)



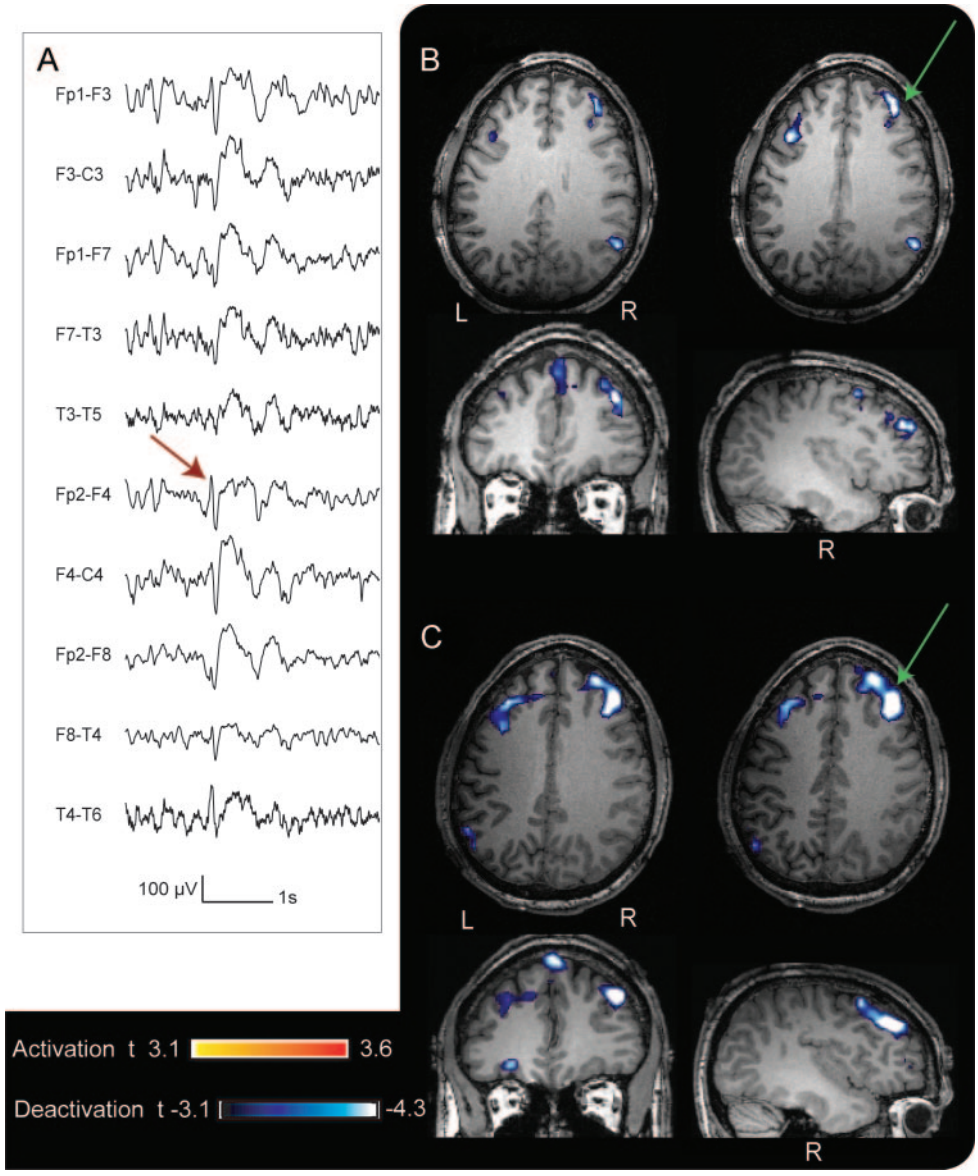
The marked events were F7-T3 spikes (referential montage) and the blood oxygen level–dependent response showed a neocortical activation in the first temporal gyrus. This response was considered concordant with the spike field but not contributory. Because of the MTS, the patient had independent validation information, but the response was invalidated.

DISCUSSION We present the results of a consecutive series of representative patients selected from a larger population being evaluated for epilepsy surgery. BOLD responses occurred in all patients having IEDs during scanning (33 of 43 patients). This rate is higher than that in previous studies,[14,15] in which the rate was approximately 50%. We explain these results by the fact that this is the first large patient group scanned at 3 T. We recently demonstrated the intrasubject reproducibility of EEG/fMRI and showed higher sensitivity for 3 T over 1.5 T, as expected from higher magnet strength.[16,17]

Considering the 33 patients with active EEG during EEG/fMRI, the BOLD response was concordant with the spike field in 88% (29 of 33 patients; 81% of the analyzed IEDs). This represents a higher proportion of concordant responses than reported earlier.[14,15] This improvement is probably explained by the use of multiple hemodynamic response functions in the fMRI analysis and by a high-field 3-T scanner. Defining spatial concordance is subjective and evaluating concordance between the BOLD response and EEG is an old problem in EEG/fMRI.[18] We considered BOLD responses concordant if the maximum *t* value corresponded to the localization of the EEG spike field, placing this comparison in a practical clinical context. As reported,[4] the BOLD changes we measured were often more extensive than expected from electroclinical findings. We reported all responses as suggested previously.[18] As hypothesized previously[1] distant or diffuse activations could be part of an epileptic network remote from the focus.

In 64% of patients with active EEG (50% of analyzed IEDs), the BOLD response contributed to the definition of the interictal epileptic focus: in all patients with neuronal migration disorders, in 50% of

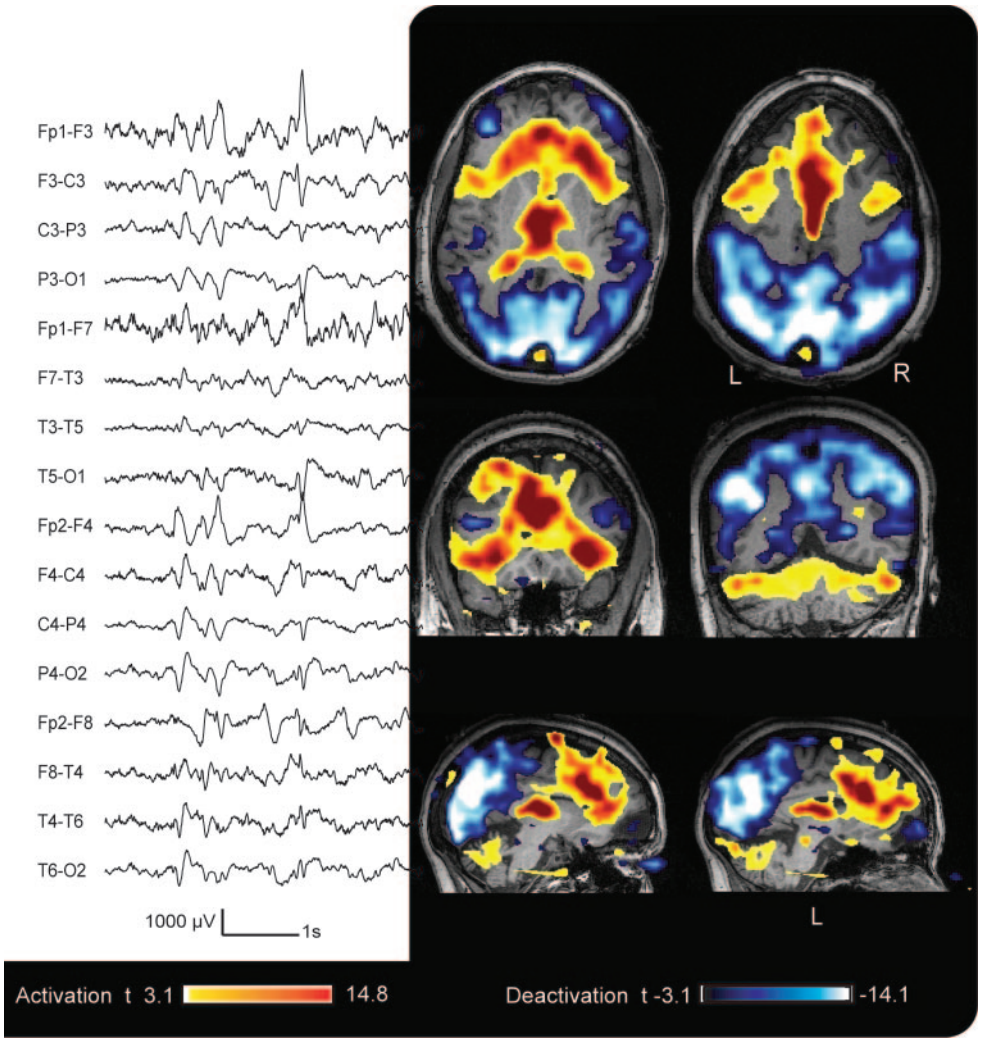
Figure 4 A 32-year-old patient (patient 24) with right hemimegaloencephaly in a hypomelanosis of Ito



(A) The marked events were bifrontal spike and wave complexes (bipolar montage), sometimes prevalent on the right side. The blood oxygen level–dependent (BOLD) response showed in 2 different scans (B and C), for the same type of interictal epileptic discharges, deactivation in the anterior part of the middle frontal gyrus bilaterally, but prevalent on the right side (the green arrow indicates the maximum T value). This BOLD response was considered concordant to the spike field and contributed to a better localization of the epileptic focus compared with the scalp EEG. The results of the second examination were concordant with those of the first. Although this is not a validation, it is worth noting that a second EEG/fMRI study in this patient revealed the same BOLD response.

patients with MTS, and in 55% of patients with epilepsy from an unknown cause. Because of the low number of patients, we cannot draw a conclusion regarding the absolute value of our findings; larger patient groups with different etiologies are needed. The high rate of a contributory BOLD response in patients with neuronal migration disorders may result from their high epileptogenicity,[19] because frequent BOLD responses occur in different types of dysplasia.[20] In addition, in 2 of 4 patients with MTS, the BOLD response was contributory, showing maximal activation in mesial temporal structures, whereas in a third patient, it showed maximum activation in temporal neocortex and in the fourth the BOLD response suggested an artifact. Because temporal spikes recorded from the scalp are primarily generated in temporal neocortex,[21,22] how can we observe a mesial activation and not a predominant neocortical response? We hypothesize that the maximum BOLD response corresponds to the source of the epileptic discharge, with a lesser or no response where the spike propagates. This may be analogous to ictal

Figure 5 A 39-year-old patient (patient 27) with frontal lobe epilepsy and bifrontal encephalomalacia



The marked events were bursts of bilateral diffuse spike and wave complexes prevalent over the anterior head regions (bipolar montage). The blood oxygen level–dependent (BOLD) response indicated activation and deactivation patterns suggestive of generalized discharges. This BOLD response was considered concordant but not contributory because it did not add new information to the scalp EEG.

SPECT, for which blood flow is usually higher in seizure-onset than in propagation regions.[23] Therefore, it may be concluded that temporal neocortical spikes with maximum mesial responses are indeed dependent on a more intense neuronal discharge in mesial temporal structures. In the third patient with MTS with a neocortical activation, we could infer that the main epileptogenicity was neocortical and not mesial.

The BOLD response was contributory in 55% of patients with epilepsy from unknown cause. The potential clinical use of these finding is the a posteriori detection of occult lesions by reviewing MRI studies and possible help in guiding electrode implantation. In particular, in these cases the results have to be interpreted in the context of clinical and electrographic information[24] and integrated with other diagnostic techniques. Surgical outcome data were not used to assess the contribution of BOLD responses, because this study investigates the irritative zone, an important aspect in the evaluation of the epileptogenic zone, but not equivalent to it.

The positive validation in 86% of patients suggests that BOLD responses could also provide valid results in patients without independent validation. Both patients with invalidated BOLD responses had MTS (patients 13 and 15). In patient 13, the BOLD response, although invalidated, was concordant with the spike field (the first showing neocortical temporal activation with ipsilateral MTS). In patient 15, the BOLD response was suggestive of an artifact.

Three-quarters of patients yielded interpretable data: of these, 88% showed concordant findings and 64% contributory findings; thus, EEG/fMRI was

contributory in half of patients initially selected. Unlike EEG source analysis[22] (figure 2), which refines EEG localization but can only use information provided by scalp EEG, EEG/fMRI includes information about structures not detectable with scalp EEG, because they are too deep (thalamus and hippocampus) or because they do not generate synchronized activity (e.g., default mode response). It would nevertheless be valuable to compare EEG source analysis results, particularly if obtained from dense electrode array, with BOLD results. We did not have such data. We propose this technique as a useful clinical tool to improve focus localization in patients with focal epilepsy.

AUTHOR CONTRIBUTIONS

Dr. Pittau: drafting/revising the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data; acquisition of data; statistical analysis. Dr. Dubeau: drafting/revising the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. Dr. Gotman: drafting/revising the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data; study supervision or coordination; obtaining funding.

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DISCLOSURE

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